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(54) Title: USE OF LYSOSOMAL ACID LIPASE FOR TREATING ATHEROSCLEROSIS AND RELATED DISEASES

(57) Abstract: The present invention comprises a method to diminish and/or eliminate atherosclerotic plaques, in mammals, through direct and indirect treatment of these plaques, in situ, using suitable substances which are capable of lipid removal, primarily through hydrolysis, either by a catalytic or stoichiometric process, wherein the substance targets receptors in and/or on the cell which lead to uptake into the lysosome. Such substances used to diminish and/or eliminate atherosclerotic plaques are generally comprised of lipid hydrolyzing proteins and/or polypeptides.

INTERNATIONAL SEARCH REPORT

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get	ESCARY, JEAN-LOUIS ET AL: "Hormone-sensitive lipase overexpression increases cholesteryl ester hydrolysis in macrophage foam cells" ARTERIOSCLER., THROMB., VASC. BIOL. (1998), 18(6), 991-998, XP002168196 * see abstract and page 997 last paragraph *		1-6, 8-24, 26-39, 41-51, 53-56, 58-62, 64-68
Y	SHERIFF ET AL.: "Characterization of lysosomal acid lipase by site-directed mutagenesisand heterologous expression." J. BIOL. CHEM., vol. 270, 1995, pages 27766-27772, XP000986290 * see abstract and page 27771 left col. *		1-6, 8-24, 26-39, 41-51, 53-56, 58-62, 64-68
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X Fu	rther documents are listed in the continuation of box C.	Patent family members are listed	I III GAINGA
"A" documents of the constant	nent defining the general state of the art which is not idered to be of particular relevance or document but published on or after the international date nent which may throw doubts on priority claim(s) or his cited to establish the publication date of another too nor other special reason (as specified) ment referring to an oral disclosure, use, exhibition or treasons	T* later document published after the int or priority date and not in conflict with cited to understand the principle or the invention X* document of particular relevance; the cannot be considered novel or cannot involve an inventive step when the day of document of particular relevance; the cannot be considered to involve and document is combined with one or not ments, such combination being obvious the art. 8* document member of the same pater	claimed invention to the considered to the considered to ocument is taken alone claimed invention inventive step when the nore other such docu-ous to a person skilled
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C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	the second party of the selection party party of the selection of the sele	Relevant to claim No.
Y	DU HONG ET AL.: "Two polymorphic forms of human lysosomal acid lipase have different level of activity." AM. J. HUMAN GENET., vol. 57, 1995, page A178 XP000996468	1-6, 8-24, 26-39, 41-51, 53-56, 58-62, 64-68
	* abstract *	
Υ	DU HONG ET AL.: "Targeted disruption of the mouse lysosomal acid lipase gene: long-term survival with massive cholesteryl ester and triglyceride storage." HUMAN MOLECULAR GENETICS., vol. 7, 1998, pages 1347-1354, XP000996474 * see abstract and page 1347 right col. *	1-6, 8-24, 26-39, 41-51, 53-56, 58-62, 64-68
X	READER ET AL.: "Expression of adenoviral vector containing the cDNA for human lysosomal acid lipase in Hela and Wolman cells." FASEB J.,	51,53, 54,56, 58,59
Υ	vol. 10, 1996, page A233 XP000996487 * abstract *	1-6, 8-24 35 - 26 39, 41-51, 53-56, 58-62, 64-68
X	"Sigma Chemie, product catalogue: Biochemikalien, organische Verbindungenund Diagnostika." 1996 , SIGMA CHEMICAL CO. XP002168197 * see page 271, products C9281, C9406 and C1403 *	[35-31]-39, 41,49,50